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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,143	09/24/2001	Brenda F. Baker	RTS-0266	5066

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EXAMINER

SCHULTZ, JAMES

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Feb

Office Action Summary

Application No.

09/960,143

Applicant(s)

BAKER ET AL.

Examiner

J. Douglas Schultz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 4-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Response to Arguments

Applicant's election with traverse of SEQ ID NO: 3 in Paper No. 5, filed January 29, 2002 is acknowledged. The traversal is on the ground(s) that since the subject antisense oligonucleotide sequences all modulate a common structure, that is, interleukin-8, that they are not novel and unobvious over each other as outlined in the restriction requirement. This is not found persuasive. In response, it is reiterated that each sequence functionally modulates its target to varying degrees as evidenced in applicants' table 1 and thus has its own activity profile, and each sequence has a unique nucleotide sequence that requires a unique search. Accordingly, each oligonucleotide sequence is considered to be a separate invention in accordance with the restriction requirement referenced above.

The requirement is still considered proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 11 is drawn to a compound 8 to 50 nucleobases in length that specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding interleukin-8.

The specification as filed contains only a general definition of the term “active sites”; it does not clearly provide a description of the actual active sites that are targeted by the invention of the instant application. Additionally, the specification only provides that such sites are experimentally determined, and does not clearly indicate where such sites may be found in the specification as filed. Since applicant has not described such characteristics, the skilled artisan would not have been able to envision what constitutes the specific active sites as claimed in the instant application.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of interleukin-8 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of interleukin-8 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of interleukin-8 in cells or tissues comprising contacting said cells or tissues with antisense compositions that inhibit the expression of interleukin-8. The claims of the above invention are also drawn to methods of treating an animal having a condition associated with interleukin-8, wherein said compositions are administered to animals such that expression of interleukin-8 is inhibited, wherein said condition may be a hyperproliferative disorder including cancer which may be lymphoma, or is an autoimmune disorder. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification teaches a method of using the claimed compositions to inhibit the expression of interleukin-8 in cells *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;

- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: “gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable” (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, “it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that “internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules” (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence

and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, “[o]ligonucleotides must be taken up by cells in order to be effective. . . . several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency” (Page 378). “[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations.” (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; “even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death. . . . oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism” (Pg. 4503, para. 1 and 2). Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “[i]mmune stimulation is widely recognized as an undesirable side-effect. . . . the immunostimulatory activity of a phosphorothioate-modified

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oligonucleotide is largely unpredictable and has to be ascertained experimentally” (page 493, right column).

Further, Branch reasons that “the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available” (Page 46, second column). Tamm et al. concludes by stating that until “the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.”

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of interleukin-8 expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with interleukin-8 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art

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associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing any condition or disease suspected of being associated with interleukin-8 expression in humans. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

A person shall be entitled to a patent unless –

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102(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by any of Blaser et al. (U.S. Patent Number 5,527,678), Daly et al. (U.S. Patent Number 5,789,539), Emmett et al. (WO 96/39536), or Malefyt et al. (U.S. Patent Number 5,833,976).

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridizes with and inhibits the expression of interleukin-8.

SEQ ID NO: 8 of Blaser et al., SEQ ID NO: 40 of Daly et al., SEQ ID NO: 9 of Emmett et al., and SEQ ID NO: 42 of Malefyt et al. all possess 100% identity with residues 358-392, 351-387, 119-149, and 358-390, respectively, of SEQ ID NO: 3 of the instant application, and would thus specifically hybridize with il-8 of SEQ ID NO: 3. Although this reference does not specifically teach the inhibition of il-8 as claimed in the present application, the sequence is substantially identical to applicant's claim and is thus considered to possess the functional limitation of inhibiting expression in the absence of evidence to the contrary. Support for this conclusion is drawn from M.P.E.P. § 2112;

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

In showing that the compounds listed above are substantially identical to applicant's claimed compound and is thus considered to possess the functional limitation of inhibiting expression, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compounds of the prior art as stated lies with the applicant, as per M.P.E.P. § 2112.01:

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of claims 1 and 2 of the instant application are considered anticipated and/or obvious as outlined above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 8, 9, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nyce, J (WO 99/13886).

Claims 1, 2, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Arici et al. (J. Clin. Endocr. and Metab., 1998. 83(4) 1201-5)

Claims 1, 2, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Pietrzkowski et al. (U.S. Patent Number 6,017,898).

Claims 1, 2, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyamoto et al. (Canc. Immunol. Immunother. (1998) 47:47-57).

The invention of the above claims is drawn to antisense compounds that target il-8, or said compounds comprising internucleoside, or nucleobase modifications or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Arici et al., Pietrzkowski et al., Miyamoto et al., and Nyce et al. all teach antisense compounds and methods that target il-8 and inhibit its expression. Furthermore, Nyce et al., teach said compounds comprising internucleoside, or nucleobase modifications or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Matsushima et al. (J. Exp. Med. 1988. 167:1883-1893), Arici et al., Pietrzkowski et al., Miyamoto et al., or Nyce et al. in view of Taylor et al., and Baracchini et al.

The invention of the above claims is drawn to antisense compounds that target il-8, or said compounds comprising internucleoside, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Matsushima et al. teach the cDNA sequence encoding il-8. Matsushima et al. does not teach antisense sequences comprising internucleoside, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents or delivery systems thereof.

Arici et al., Pietrzkowski et al., Miyamoto et al., and Nyce et al. all teach antisense compounds and methods that target il-8 and inhibit its expression. Furthermore, Nyce et al., teach antisense compounds comprising internucleoside, and nucleobase modifications or compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Arici et al., Pietrzkowski et al., Miyamoto et al., do not teach antisense sequences comprising linkage, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents or delivery systems thereof, and Nyce et al. do not teach said compounds comprising sugar or chimeric modifications.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate the methods necessary to achieve gene inhibition.

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence of Matsushima et al. (identical in sequence to applicant's SEQ ID NO: 3, but 78 nucleotides shorter) to generate antisense sequences as taught by Arici et al., Pietrzkowski et al., Miyamoto et al., or Nyce et al. for inhibition of il-8 expression, and further, it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini et al. into said antisense compounds. One would have been motivated to create such compounds because Arici et al., Pietrzkowski et al., Miyamoto et al., or Nyce et al. expressly teach antisense compounds that target and hybridize to il-8 (applicants' SEQ ID NO: 3). One would have been motivated to modify said antisense compounds as taught by Baracchini et al., because Baracchini et al. teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
April 4, 2003


KAREN LACOURCIERE
PATENT EXAMINER